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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,311	12/12/2003	Steven M. Ruben	PF155C1P1DI	8060

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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,311	RUBEN ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 13-34* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152. .

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/05/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant amendment to the claims, filed 05 May 2006 has been received and entered. Claims 1-9 and 11-12 have been canceled and claims 13-34 have been added.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 05 May 2006 is acknowledged. The traversal is on the ground(s) that a search of the claims of any of the groups would also provide useful information for the claims of the other groups, therefore, the combined search and examination of such compositions would not entail a serious burden. This is not found persuasive because M.P.E.P. § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner. MPEP (808.02) indicates that a serious burden of search can be established by separate classification of the inventions which shows that each invention has attained recognition in the art as a separate subject for inventive effort and also a separate field of search. Such separate classification was set forth in the previous Office action mailed and a *prima facie* case of serious burden of search has been established. Furthermore, Applicant has offered no evidence to rebut this showing.

Applicant's comments regarding the species election are persuasive in so far as the newly submitted claims do not encompass the mutations of the previously filed claims. Therefore, the species election requirement is moot and withdrawn. Applicant

should note that if the claims are amended to include the various different mutational variants, the species election may be reinstituted.

The requirement is still deemed proper and is therefore made FINAL.

Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05 May 2006.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The use of the trademark FLAG® has been noted in this application (see at least page 55 at [0182]). It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicant should also review the entire specification to make sure all trademarks are referenced appropriately.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22 and 33 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter.

Claims 22 and 23, as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught in specification. Applicant should point to the page and line number to support any amendment to the claims. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 16-24, 27-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement of claims 13, 17-24, 28-34 requires availability of the specific sequences claimed therein. This determination has been made because said cDNA

deposited under ATCC accession number 75977 is not fully disclosed nor have they been shown to be publicly known and freely available. Specifically, the deposit statement is not complete. See MPEP Chapter 2408 Term of Deposit 37 CFR 1.806. Term of deposit. "A deposit made before or during pendency of an application for patent shall be made for a term of at least thirty (30) years and at **least five (5) years after the most recent request for the furnishing of a sample of the deposit** was received by the depository. In any case, samples must be stored under agreements that would make them available beyond the enforceable life of the patent for which the deposit was made."

An affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number stating that the deposit shall be made for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposit.

Claims 22-23 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses vectors and host cells comprising a polynucleotide encoding proteins of SEQ ID NO:2 (see pages 149-161). Also disclosed at page 188

are administration of cells to a patient wherein the cells have been engineered with a polynucleotide *ex vivo* (see [0478]) as well as *in vivo* (see [0479]). Based on this disclosure, the Examiner has interpreted the claims as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that KGF-2 gene products (SEQ ID NO: 1) can be expressed in vivo and that methods of doing such "should be apparent to those skilled in the art". However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated KGF-2 gene of SEQ ID NO: 1 (or encoding SEQ ID NO:2, or some variant thereof) is demonstrated to express the KGF-2 peptide. The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col. 1, 2nd full paragraph; pg 3182-3183). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, it would have required undue experimentation for the skilled artisan to have made any

and all transgenic non-human animals according to the instant invention. Thus, based on the art recognized unpredictability of producing transgenic animals, and in view of the lack of guidance provided by the specification for producing a transgenic animal, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals.

The specification also discloses that polynucleotides encoding KGF-2 products can be used to genetically engineer host cells to express such products *in vivo* and that these products can be used in gene therapy approaches for the modulation of KGF-2 expression. However, the specification does not teach any methods or working examples that indicate a KGF-2 nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the KGF-2 nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the

DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a KGF-2 nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a KGF-2 nucleic acid in the cell of an organism or be able to produce a KGF-2 protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the KGF-2 protein and to introduce and express a KGF-2 nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce a KGF-2 nucleic acid in the cell of an organism to be able produce that KGF-2, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Double Patenting

37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their

retention during pendency in more than one application. It is noted that Applicant has several applications pending which contain common subject matter, related to KGF-2. Applicant is reminded to maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 342-351, 353-359, 361-367, 369-375, 377-383, 385-391, 393-399, 401-407, 409-415, 417-423, 425-430, 432-436, 438-444, 446-452, 454-460, 462-468, 470-476, 478-484, 486-492, 494-500, 502-508, 510-516, 518-524, 526-531, 533-539, 541-546, 548-554, 556-561, 563-569, 571-576, 578-584, 586-592, 594-601, 603-608, 610-616, 618-623, 625-629, 631-637, 639-645, 647-

652, 654-659, 661-666, 668-674, 676-682 of U.S. Patent No. 6,077,692. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass common subject matter; i.e. encoding a polypeptide of SEQ ID NO:2. The claims of the instant application are directed to polynucleotides encoding a polypeptide which is 95-97% identical to a polypeptide of SEQ ID NO:2, wherein the polypeptide stimulates proliferation of epithelial cells. Embodiments of these claims would encompass those molecules of '692 and there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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